REMARKS

Restart of the period for filing a response

In an Office Communication mailed June 22, 2009, the USPTO acknowledged that due to a glitch in the E-Office Action pilot program, the Office Action mailed June 9, 2009 was improperly loaded (missing references). Accordingly, the time period for filing a response to the Office Action was reset to start from the mailing date of the notification, i.e., June 22, 2009, not the mailing date of the Office Action. Insofar as the present reply is being filed within the first-three months of the reset date, this response is considered timely.

However, if necessary, the Commissioner is authorized to charge any fees associated with this response to Deposit Account No. 13-3402.

Claims

Claims 1–19 are currently pending of which claims 10–12 and 18–19 are under examination pursuant to the restriction requirement mailed March 31, 2008.

Claims 1–9 and 13–17 are withdrawn from consideration pursuant to the aforementioned restriction/election.

Claim 20 is added by this paper.

Claim amendments

New claim 20 reads on the elected species and is supported by the disclosure contained in, for example, paragraph [0018] of the published US application No. 2007-0154496 and the information provided in the sequence disclosure.

Applicants respectfully submit that the amendments presented herein complies with the requirements set forth under CFR §1.116. For example, the polypeptides of new claim 20 are identified by their sequence identifier numbers and differ from examined claim 1 by the transitional phrase consisting of. No new sequences are added and a search of the recited sequences has already been performed by the Examiner. It is further submitted that the amendments do not raise new matter. Entry thereof is earnestly solicited.

Rejections under §102

Claims 10–12 and 18–19 are rejected under §102(b) as allegedly anticipated by Bose

(*Immunology*, 1998), Zhou (*Immunology*, 1995), Gefter (USP 6,759,234) or Gefter (WO 96/07428). These rejections are respectfully traversed.

The PTO's contentions are as follows:

13. Claims 10-12 and newly added claims 18-19 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent 6,759,234 (PTO-892; Reference A) for the same reasons set forth in the previous Office Action mailed 9/30/08.

14. Claims 10-12 newly added claims 18-19 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Bose et al. (PTO-892; Reference W) for the same reasons set forth in the previous Office Action mailed 9/30/08.

15. Claims 10-12 newly added claims 18-19 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Zhou et al. (PTO-892; Reference V) for the same reasons set forth in the previous Office Action mailed 9/30/08.

16. Claims 10-12 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. WO 96/07428 (PTO-892; Reference N) for the same reasons set forth in the previous Office Action mailed 9/30/08.

The art rejections under §102 are based on the references' disclosure of the term Lol p 4 polypeptide. The Office Action has not established that such polypeptides are structurally and/or identical to the polypeptide(s) encoded by SEQ ID NO: 1 or SEQ ID NO: 3, as claimed herein. More specifically, the totality of the disclosure in the aforementioned references says nothing about the identity of the polypeptides of the present invention which are currently claimed. Absent such, the references cannot anticipate what is claimed herein.

As an example, posted below are results of the search report carried out on September 22, 2008, which was used in the non-final rejection mailed September 30, 2008. The top ten matching sequences are displayed:

SUMMARIES

Result No.	Score	% Query Match	Length	DB	ID	Description
1	2264	95.9	423	10	AEB13456	Aeb13456 Lolium pe
2	2264	95.9	500	10	AEB13458	Aeb13458 Lolium pe
3	2119	89.7	500	8	ADI44454	Adi44454 P. praten
4	2119	89.7	500	10	AEB13460	Aeb13460 Phleum pr
5	2119	89.7	500	10	AEB28062	Aeb28062 Phleum pr
6	2087	88.4	500	8	ADI44452	Adi44452 P. praten
7	2087	88.4	500	8	ADI44450	Adi44450 P. praten
8	1948	82.5	518	10	AEB28056	Aeb28056 Hordeum v
9	1926.5	81.6	518	10	AEB28052	Aeb28052 Secale ce
10	1921	81.3	518	10	AEB28058	Aeb28058 Triticum

In the "alignment analysis" which follows the aforementioned table, it is further

acknowledged that among these top-matching sequences, *only* the polypeptides encoded by AEB13456 (423 amino acids) and AEB13458 (500 amino acids) are identical to the instantly claimed polypeptide of SEQ ID NO: 2 and SEQ ID NO: 4, respectively. These reference polynucleotides are disclosed in WO 2005-058936 to Feibig et al. Coincidentally, WO 2005-058936 is the WIPO publication of the international application PCT/EP2004/013663 (PCT '663) and the present application is the US national phase of PCT '663. It is clear that none of the other sequences encodes the claimed polypeptide sequence of SEQ ID NO: 2 or SEQ ID NO: 4. To this end, the next top-matching sequence of ADI44454 encodes a protein that has 96.2% sequence identity to the claimed SEQ ID NO: 4 (16 mismatches). See the "Alignment Scores" section of RESULT 3 in the search report of September 22, 2008. Thus it is clear, at least based on the results of the sequence search, that the claimed polypeptides are both novel and unobvious over the art-known proteins.

It is by now well-established that "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." See MPEP §2131 and further corroborated by the Fed. Circuit's decision in *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). With respect to inherency, the Courts have established that "the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). Inasmuch as the cited Gefter et al., Bose et al., Zhou et al, and WO 96/07428 say nothing about Lol p 4 polypeptide sequences and the Examiner has not established that the Lol p 4 polypeptide disclosed therein necessarily comprises the sequences recited herein, the rejection is without legal merit.

Applicants further submit that for anticipation, "the identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The Office Action fails to establish that the polypeptides disclosed in the aforementioned references contain the **complete** Lol p 4 polypeptide sequence as presently claimed. To this end, Applicants enclose an exhibit (EXHIBIT A) which demonstrates that a search of the term Lol p 4 in NCBI's protein database results in the identification of at least four Lol p 4 variants (accession Nos. CAH92637, CAJ18067, CAJ18069

and CAJ18068) and a fragment sequence (accession No. A60737). It cannot be ascertained whether the reference teaches a sequence that is completely different from what is claimed in the present application. More importantly, it is clear that the cited references of Bose, Zhou, Gefter (USP 6,759,234) and Gefter (WO 96/07428) fail to provide "a complete detail" (i.e., the polypeptide sequence) of the claimed invention. As such, an inherency rejection under §102/§103 is not supported and should be withdrawn. See MPEP §2112.

Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. §112, ¶1

Claims 10–12 are rejected due to allegedly lacking enablement with respect to the use of the polypeptides of the present invention as pharmaceutical compositions. This rejection is respectfully traversed.

Enablement

In the paragraphs bridging pages 5 and 8, the Office Action alleges that the pharmaceutical compositions are non-enabled. This contention is respectfully traversed.

Applicants' specification, coupled with a skilled worker's knowledge, provides more than adequate guidance on how to make the claimed polypeptide molecules and use pharmaceutical compositions and medicaments comprising such polypeptides for immunotherapy. The specification provides both general and specific guidance regarding the specific epitopes in allergens and how such could be manipulated for reliable hyposensitisation. See, for example, the disclosure contained in the paragraphs bridging pages 6 and 7 of the instant specification and the reference article by Schramm et al., 1999, *J. Immunol.* 162: 2406-2414. With respect to DNA vaccines, the specification explicitly teaches that "experimental evidence of allergen-specific influencing of the immune response has been furnished in rodents by injection of allergen-encoding DNA (Hsu et al., 1996, *Nature Medicine* 2 (5): 540-544)." Furthermore, the specification of the present application discloses specific immunotherapy or desensitization as therapeutic field for especially recombinant allergen proteins with higher purity and therefore reduced side effects than allergen proteins isolated from natural sources which are always mixtures of compounds. To this end, the specification discloses strategies to minimize the risks of side effects with the development of T-cell reactive fragments with reduced or no IgE-reactivity leading to hypoallergenic peptides (see, page 8, lines 15–26). The screening for T-cell

and IgE epitopes were common knowledge at the priority date of the present application. Thus, a person skilled in the art would have been able to identify T-cell and IgE epitopes and produce hypoallergenic peptides. Nevertheless, also the classic approaches of specific immunotherapy and desensitization were applicable as a skilled person would have known the pharmaceutical effects and also the side effects and risks of an allergen protein administered to a patient and would have followed clinical recommendation protocols for specific immunotherapy and desensitization.

In relation to an enabling disclosure on the utilization of grass pollen allergen polypeptides in treatment of subjects, the specification provides a detailed disclosure for the design, synthesis and use of recombinant allergen extracts with reduced IgE reactivity. See, for example, the last paragraph on page 6 of the originally-filed specification. To this end, the Examiner is also courteously invited to review the disclosure contained in Focke et al., which was submitted with the previous Reply (Focke et al., *FASEB Journal*, 15, 2042-44, 2001). As evidenced by the disclosure in the "Principle Findings" section of Focke and the immunoglobulin reactivity data provided in Table 1, it is respectfully submitted that as of the filing date of the present application, the instantly claimed grass pollen allegens could be routinely manipulated and utilized as pharmaceutical preparations in a manner recited in the claims.

Thus it is respectfully submitted that the specification provides an enabling disclosure on the claimed allergenic properties of the recombinant, grass pollen allergen polypeptides of the instant invention. Therefore, the specification's express teaching that the claimed compounds are pharmaceutically useful is clearly credible as required. The PTO's contentions regarding non-enablement are especially weak in view of the detailed disclosure contained in Applicants' own specification and the state of the art before the earliest filing date of the instant application. Withdrawal of the rejection is respectfully requested.

To support the contention of non-enablement, the Office Action cites Tarzi (*Expert Opinion in Biol. Ther.*, 2003) to allege that "whole allergen immunotherapy is unpredictable." However, even Tarzi discloses the therapy of allergic diseases with specific immunotherapy or desensitization in general being effective and successfully applied for many years. See, the last paragraph at page 617 of the cited reference. Moreover, in Gefter et al. (USP 6,795,234), which was cited by the PTO in reference to an art rejection, the complete third and fourth paragraphs in the "BACKGROUND OF THE INETNION" (especially, col. 1, lines 26–45) discloses that the risk of systemic reactions like anaphylactic shock can be effectively minimized in individuals via

specific immunotherapy, wherein pharmaceutical compositions comprising allergen polypeptides and/or vaccines comprising DNA sequences which encode such polypeptide allergens are utilized. As such, the PTO's contentions of non-enablement, based on the disclosure contained in Tarzi and/or Gefter is without merit.

The Office Action at page 6 alleges that it would "take undue trials and errors to practice the claimed invention." These allegations, however, do not present any evidence to doubt the objective enablement of Appellants' disclosure. As clearly and succinctly stated by the court in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> As a matter of Patent Office practice, then a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must** be taken in compliance with the enabling requirement of the first paragraph of §112, **unless** there is reason to doubt the objective truth of statements contained therein relied on for enabling support. (emphasis in original)

Furthermore, as stated in *Marzocchi*, at 370, the PTO must have adequate support (evidence or reasoning) for its challenge to the credibility of Appellants' statements of enablement. Thus, in the absence of evidence which demonstrates otherwise, the claims must be taken to satisfy the requirements of 35 U.S.C. § 112, ¶1.

Working examples are not required to establish enablement. As stated by the court *Marzocchi*, at page 369:

> The first paragraph of §112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.

The assertion of undue experimentation in the rejection is merely conclusory. Further, as discussed above, the specification provides more than sufficient guidance to make and use the claimed medicaments and/or pharmaceutical compositions using no more than routine experimentation. Finally, a high level of skill does not establish that one skilled in the art would have reasons to doubt the veracity of the statements in Appellants' specification with respect to the use of the claimed composition in the diagnosis, treatment, and/or prevention of the claimed conditions.

Based on the aforementioned remarks and arguments, further in view of the amendments presented herein, it is respectfully submitted that Applicants' specification provides an enabling disclosure of what is claimed by the present invention. Withdrawal of the rejection under 35 U.S.C. §112, ¶1, is respectfully requested.

In view of the above remarks, favorable reconsideration is courteously requested. If there are any remaining issues which could be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below.

Respectfully submitted,

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